REMARKS

Claims 40-78 are pending in this application. Claims 1-39 have been cancelled without prejudice or disclaimer. Claims 40-78 have been added.

Claims 40-58 have been added to claim the subject matter contained in claims 3-12, now cancelled, in proper US form. Claims 59-78 have been added to claim the subject matter contained in claims 30-39, now cancelled, in proper US form. Support for the amendment can be found throughout the specification and the claims as originally filed, for example, paragraphs [0021] and [0027] at page 3, paragraphs [0029] and [0032] at page 4, paragraph [0034] at page 5 and original claims 1-12 and 30-39.

The amendments are for the sole reason of advancing prosecution. Applicants, by amending or cancelling any claims, make no admission as to the validity of any rejection made by the Examiner against any of these claims.

No new matter has been introduced to this application within the meaning of 35 U.S.C. §132.

In view of the following, further and favorable consideration is respectfully requested.

I. Objections to claims 2-12

Applicants respectfully submit that claims 2-12 have been cancelled making the objections moot. The subject matter contained therein are covered by new dependent claims 42-58, which properly limit the subject matter of claim 40 on which

they depend and comply with the requirements for dependent claims under 37 CFR 1.75(c).

In addition, claim 44 correctly recites the terms “ciglitazone” and “rosiglitazone.”

Accordingly, withdrawal of the objections is respectfully requested.

II. Rejection of Claims 1-12 and 30-39 under 35 U.S.C. §101 and §112, second paragraph

Applicants respectfully submit that rejected claims 1-12 and 30-39 have been cancelled, and added as new claims 40-78 in proper US format in accordance with 35 USC §101 and definite within the meaning of 35 USC §112, second paragraph.

Withdrawal of the rejections is therefore respectfully requested.

III. Rejection of Claims 3-12 under 35 USC §102(b)

The Examiner has rejected claims 3-12 under 35 USC §102(b) as being anticipated by Mehta, R.G. et al. (Journal of the National Cancer Institute, 2000).

As mentioned, claims 3-12 have been cancelled, and corresponding new claims 40-58 are pending in this application, and therefore Applicants herein respectfully traverse this rejection for claims 40-58.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal*

Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond,* 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

Applicants submit that pending claims 40-58 are not anticipated by Mehta et al. since the reference fails to teach each and every element of the claims.

Claims 40-58

Independent claims 40 and 41, respectively, are directed to a method for diagnosing and treating ***NIS gene-expressing*** carcinomas, metastases of carcinomas or both thereof comprising administering (i) at least one PPAR-γ ligand, (ii) at least one ligand selected from the group consisting of RAR ligand and RXR ligand, and (iii) ***a substance that is actively transported by the NIS symporter*** into the cells of carcinomas or metastases, ***wherein the uptake of the substance which is actively transported by the NIS symporter is stimulated or enhanced by means of induction of NIS gene expression in the cells***.

These methods are based on the finding that the sodium-Iodide symporter (NIS) expression and the cellular uptake of a substance that is actively transported by the NIS can be synergistically enhanced by administering a specific ligand combination, i.e., a combination of at least one PPAR-γ ligand and at least one RAR

and/or RXR ligand. This synergism is considered due to heterodimerization of the PPAR-y receptors and RAR/RXR receptors and thereby the inducement, stimulation or enhancement of the NIS gene expression. *See* paragraph [0010] at page 4 of the original specification.

It was found in the present application that synergistic endogene stimulation of the NIS gene leads to synergistically enhanced cellular uptake of the substances, such as iodide that is actively transported by the NIS. This finding can be advantageously employed in the field of diagnosis and therapy of NIS gene-expressing carcinomas, such as glandular carcinomas, like breast carcinomas. When the substance to be actively transported by the NIS is radioactive, such as radioactive iodide or technetium, this finding can be advantageously employed in the field of radio diagnosis and radiotherapy.

Accordingly, the present application discloses that the administration of a specific PPAR-y ligand, e.g., ciglitazone, abbreviated as CIG, in combination with trans-retinoic acid (tRA), synergistically enhances uptake of radioactive iodide in breast cancer cells (MCF -7 cells), in comparison to the administration of either CIG or tRA alone. *See* paragraphs [0010] to [0015] at pages 4 to 6, paragraphs [0042] to [0050] at pages 16 to 18 and Figures 1 and 2 of the original specification.

The experimental results described in the specification clearly shows that treatment of the cancer cells with CIG and tRA in combination, allows the iodide uptake, which increases 5-fold by tRA alone, to be increased 3-fold more. In other words, the iodide uptake can be increased by about 20-fold, as compared to

untreated cells. In addition, the blocking experiments using the NIS inhibitor, KCl04, clearly demonstrate that the iodide uptake into the cancer cells is specifically due to the expression of the NIS symporter. Further, the claimed diagnostic or therapeutic method is selective to the cancer cells expressing the NIS gene. *See* paragraphs [0015] and [0047] in the specification, and Figure 2 as originally filed. It was shown that no iodide uptake was induced, by way of example, in HeLa cells which do not express the NIS gene.

Mehta et al.

Mehta et al. describe that a combination of a PPAR-γ ligand, such as troglitazone and a ligand specific to a RXR receptor (LG 10068) markedly inhibits the development of mammary lesions, and thus, may be used for chemoprevention of breast cancer. *See* page 418, left column, page 420, Table 2, and "discussion" bridging pages 421 and 422.

However, Mehta et al. do not teach the administration of a substance, such as iodide or technetium which is actively transported by the NIS in order to achieve chemoprevention. In addition, Mehta et al. do not teach an endogene stimulation of a gene, particularly the NIS gene, in order to achieve chemoprevention of breast cancer. Further, Mehta et al. do not teach any effect of the ligands on the expression of the NIS gene and the uptake of the substance, such as iodine that is specifically achieved by the NIS. Thus, Mehta et al. do not recognize or teach that the uptake of a substance, such as iodide, which is actively transported by the NIS may be

synergistically enhanced by the administration of a PPAR-γ ligand and a RAR and/or RXR ligand.

In view of the foregoing, Mehta et al. fail to teach each and every element of pending claims 40-58, and thus claims 40-58 are not anticipated by Mehta et al.

Withdrawal of the rejection is therefore respectfully requested.

IV. Rejection of Claims 3-12 under 35 U.S.C. §103(a)

The Examiner has rejected claims 3-12 as being unpatentable over Mehta, R.G. et al. in view of Urban et al. (US Patent No. 5,814,647). In addition, the Examiner has rejected claims 3-12 as being unpatentable over Mehta, R.G. et al. and Urban et al., above, in view of Mandell, R.B. et al. (Cancer Research, 1999).

Applicants respectfully traverse these rejections for presently pending new claims 40-58, which correspond to rejected claims 3-13, now cancelled.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can

be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, *supra*, slip opinion at 13-15.) Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

A *prima facie* case of obviousness has not been established in the present application since none of the cited references, taken alone or in combination, fails to teach or suggest all of the limitations of the claims, as required by *In re Wilson*.

The discussion of claims 40-58 made in Section III, above, is incorporated herein in its entirety. To summarize, claims 40 and 41, respectively, are directed to a method for diagnosing and treating NIS gene-expressing carcinomas, metastases of carcinomas or both thereof comprising administering (i) at least one PPAR-γ ligand, (ii) at least one ligand selected from the group consisting of RAR ligand and RXR ligand, and (iii) a substance that is actively transported by the NIS into the cells of carcinomas or metastases, wherein the uptake of the substance which is actively transported by the NIS is stimulated or enhanced by means of induction of NIS gene

expression in the cells. The other claims of claims 42-58 are, directly or indirectly, dependent from claim 40, and thus contain all of the limitations of the claims.

Mehta et al.

The discussion of the teachings of Mehta et al., above, at page 14-15 of this paper is incorporated herein in its entirety. As discussed, Mehta et al. fail to teach the administration of a substance (e.g., iodide or technetium) that is actively transported by NIS. In addition, Mehta et al. fail to teach endogene stimulation of NIS gene, nor do they teach any effect of the ligands on the expression of NIS gene and the uptake of the substance actively transported by NIS. Thus, Mehta et al. do not teach that the uptake of a substance such as iodide which is actively transported by the NIS may be synergistically enhanced by the administration of a PPAR-γ ligand and a RAR and/or RXR ligand.

Urban et al.

Urban et al. do not remedy the deficiencies of Mehta et al. Urban et al. describe the employment of troglitazone and related thiazolidinedione compounds in the treatment of climacteric and cancer (*see*, Abstract). However, Urban et al. not only fail to teach a combination of a PPAR-γ ligand and a RAR and/or RXR ligand, but also fail to teach the additional employment of a substance which is actively transported by the NIS. Thus, Mehta et al. and Urban et al., taken alone or in combination, cannot teach claims 40-58.

In view of foregoing, Applicants submit that a *prima facie* case of obviousness

has not been established in this application by the references of Mehta et al. and Urban et al., against claims 40-58. Withdrawal of the rejection based on the references is therefore respectfully requested.

Mandell et al.

Mandell et al. cannot remedy the deficiencies of Mehta et al. and Urban et al. Mandell et al. describe a retroviral transfer of rat NIS gene into human and murine tumor cells resulting in highly significant iodide uptake (*see* page 661, right column, last paragraph above the heading "Materials and methods" in combination with the results displayed in figure 1).

However, not only do Mandell et al. fail to teach the administration of the specific combination of PPAR- γ ligand and a RAR and/or RXR ligand, but also they fail to teach the effect of the combinations on the expression of NIS gene. Actually, Mandell et al. are totally silent with respect to any effect that ligands may have on the expression of NIS gene and on a substance uptake which is from the cellular expression. Accordingly, Mehta et al., Urban et al. and Mandell et al., taken alone or in combination, fail to teach all of the limitations of the present claims. None of the cited references teach an effect of a PPAR-γ ligand and a RAR and/or RXR ligand on the expression of NIS gene and the cellular uptake of the substances, such as iodide which are actively transported by the NIS. None of the references teach that the NIS transcription and expression and the cellular uptake governed by the NIS may be synergistically enhanced by the administration of a certain ligand combination.

Accordingly, Applicants submit that a *prima facie* case of obviousness has not been established in this application by the references of Mehta et al., Urban et al., and Mandell et al., against claims 40-58. Withdrawal of the rejection based on the references is therefore respectfully requested.

CONCLUSION

In view of the remarks set forth herein, Applicants submit that that the presently pending claims are in condition for immediate allowance. Early notice to that effect is earnestly solicited. The Examiner is invited to contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

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